I.   AMENDMENTS

The following listing of the Claims replaces all prior versions, amendments and listings.

Please cancel Claims 80 and 85, without prejudice or disclaimer.

Please amend claims 56, 57, 58, 62, 76, 81, 84 and 86 as provided below.

1.   (Previously Canceled).

56.   (Currently Amended) A method for inhibiting the proliferation of a hyperproliferative <u>neoplastic</u> cell, comprising contacting the cell with a 5'-phosphoryl or phosphoramidatyl substituted prodrug of a 5-substituted pyrimidine nucleoside or nucleotide, a derivative or a metabolite thereof that is selectively converted to a toxin in the cell by an endogenous, intracellular enzyme.

57.   (Currently Amended) A method for treating a pathology characterized by hyperproliferative <u>neoplastic</u> cells in a subject comprising administering to the subject a 5'-phosphoryl or phosphoramidatyl substituted prodrug of a 5-substituted pyrimidine nucleoside or nucleotide, a derivative or a metabolite thereof that is converted to a toxin in a hyperproliferative cell by an intracellular enzyme that is endogenously overexpressed or over-accumulated in the cell.

58.   (Currently Amended) The method of claim 56, wherein the prodrug, derivative or metabolite is an L- or D- isomer of the formula:
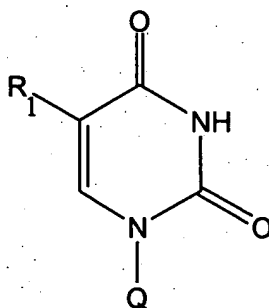
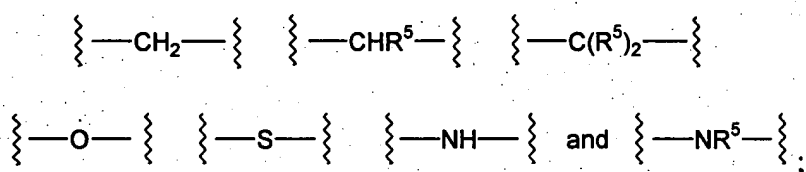wherein R_1 is ~~an electrophilic leaving group~~ <u>a substituent of the formula</u>:
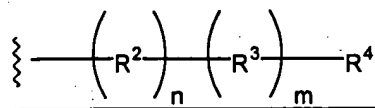
$$\xi - \left(R^2 \right)_n \left(R^3 \right)_m R^4$$

wherein R^2 is one of:

an unsaturated hydrocarbyl group;

an aromatic hydrocarby group; or

a heteroaromatic group;
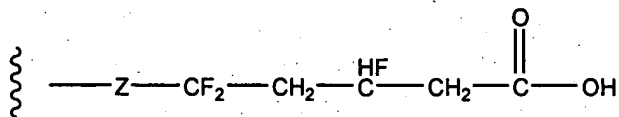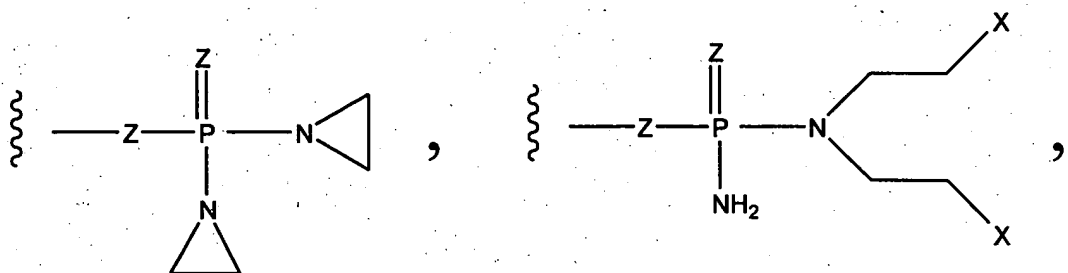
R^3 is selected from the group consisting of:

$$\xi - CH_2 - \xi \quad \xi - CHR^5 - \xi \quad \xi - C(R^5)_2 - \xi$$

$$\xi - O - \xi \quad \xi - S - \xi \quad \xi - NH - \xi \quad and \quad \xi - NR^5 - \xi ;$$
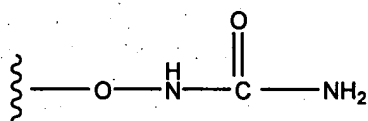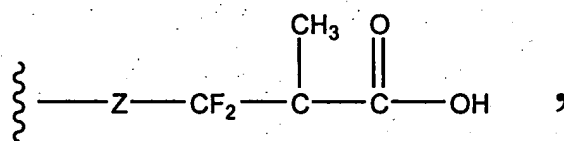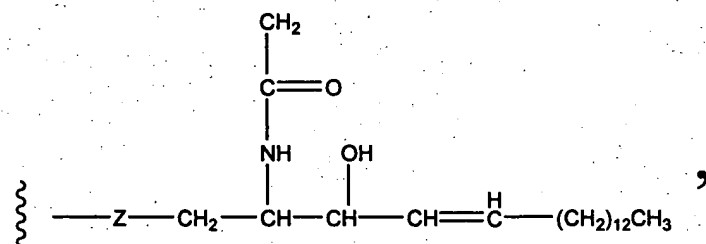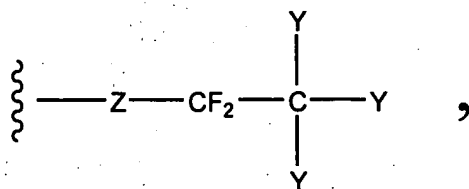
wherein R^5 may be the same or different and is independently a linear or branched alkyl group having from 1 to 10 carbon atoms, or a cycloalkyl group having from 3 to 10 carbon atoms;

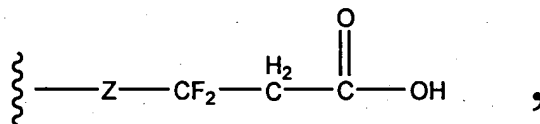wherein n is an integer from 1 to 10;

wherein m is 0 or 1;

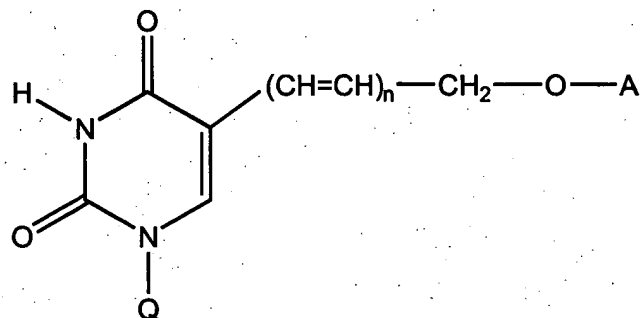wherein R^4 is a toxophore selected from the group consisting of:

$$\xi\!-\!Z\!-\!CF_2\!-\!\underset{\underset{Y}{|}}{\overset{\overset{Y}{|}}{C}}\!-\!Y \quad ,$$

$$\xi\!-\!Z\!-\!CH_2\!-\!\underset{\underset{NH}{|}}{CH}\!-\!\underset{\underset{OH}{|}}{CH}\!-\!CH\!=\!\overset{H}{C}\!-\!(CH_2)_{12}CH_3 \quad ,$$

where the NH connects to $\underset{\underset{CH_2}{|}}{C}\!=\!O$

$$\xi\!-\!Z\!-\!CF_2\!-\!\underset{\underset{C}{|}}{\overset{\overset{CH_3}{|}}{C}}\!-\!\overset{\overset{O}{\|}}{C}\!-\!OH \quad ,$$

$$\xi\!-\!O\!-\!\overset{H}{N}\!-\!\overset{\overset{O}{\|}}{C}\!-\!NH_2$$

and

$$\xi\!-\!Z\!-\!CF_2\!-\!\overset{H_2}{C}\!-\!\overset{\overset{O}{\|}}{C}\!-\!OH \quad ,$$

wherein X is -Cl, -Br, -I, or other potent leaving group, with the proviso that when R^7 is -H, and M is zero, then R^4 is not a halogen or when m is zero and n is zero, then R^4 is not a halogen;
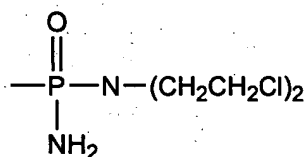
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wherein Z is independently -O- or -S-;

or a compound of the formula:

$$\text{(CH=CH)}_n\text{—CH}_2\text{—O—A}$$
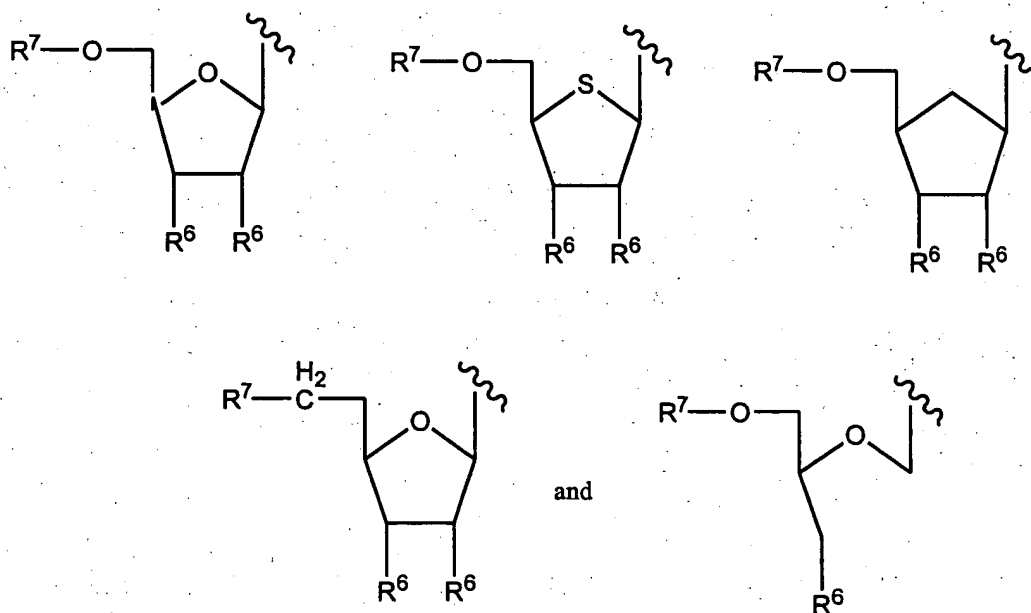
wherein n is an integer from 1 to 10; wherein A is a phosphoryl group or phosphoramidatyl group or a ~~compound~~ substituent of the formula:

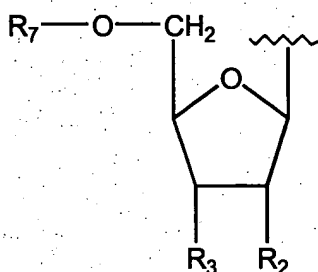$$\text{—P—N—(CH}_2\text{CH}_2\text{Cl)}_2$$

wherein Q is selected from the group consisting of:

and

wherein R^6 is independently -H, -OH, -OC(=O)CH$_3$, or -O-Rg wherein Rg is a hydroxyl protecting group other than acetyl;

wherein R^7 is hydrogen, a masked phosphate group, or a phosphoramidatyl group.

59.   (Previously Amended) The method of claim 58, wherein Q has the formula:

$$R_7—O—CH_2$$

wherein R_7 is selected from the group consisting of a masked phosphoryl moiety and a phosphoramidatyl moiety, and wherein R_2 and R_3 are the same or different and are independently -H or -OH.

60.   (Original Claim) The method of claim 58, wherein R_1 is a halogen.

61.   (Previously Amended) The method of claim 58, wherein R_1 is of the formula (-CH=CH)$_n$-R$_4$, wherein n is an integer from 1 to 10, and R_4 is selected from the group consisting of H, a halogen, alkyl, alkenyl, alkynyl, hydroxyl -O-alkyl, -O-aryl, O-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, -NH$_2$, -NH-alkyl, -N(alkyl)$_2$, -NHCHO, -OCN, -SCN, -N$_3$, -NHOH, -NHO-alkyl, and NHNH$_2$.

62.   (Currently Amended) A compound of the formula:
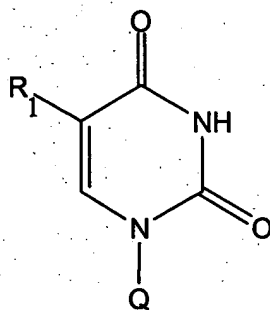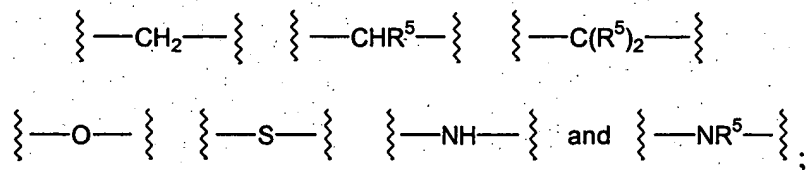

wherein:

R^1 is of the formula:
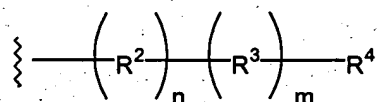
wherein R^2 is one of:

an unsaturated hydrocarbyl group;

an aromatic hydrocarbyl group; or

a heteroaromatic group;

R^3 is selected from the group consisting of:

$\{$—CH$_2$—$\}$ $\{$—CHR^5—$\}$ $\{$—C(R^5)$_2$—$\}$

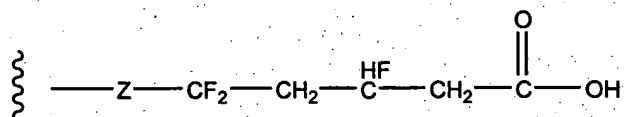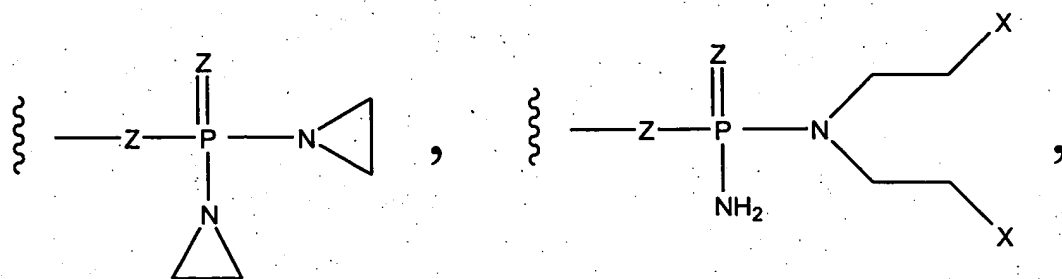$\{$—O—$\}$ $\{$—S—$\}$ $\{$—NH—$\}$ and $\{$—NR^5—$\}$;

wherein R^5 may be the same or different and is independently a linear or branched alkyl group having from 1 to 10 carbon atoms, or a cycloalkyl group having from 3 to 10 carbon atoms;
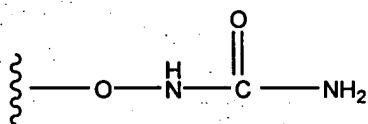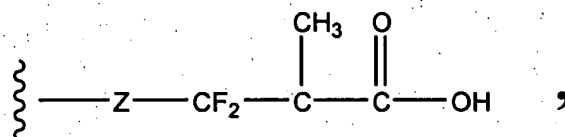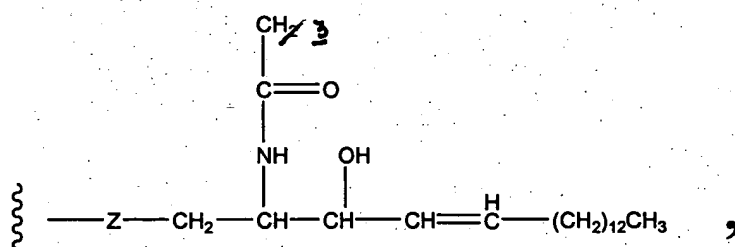
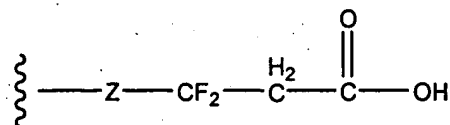wherein n is an integer from 1 to 10;

wherein m is 0 or 1;

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wherein R^4 is a toxophore selected from the group consisting of:

$$\xi - Z - \overset{\overset{\displaystyle Z}{\|}}{\underset{\underset{\displaystyle N}{|}}{P}} - N \triangle \quad , \quad \xi - Z - \overset{\overset{\displaystyle Z}{\|}}{\underset{\underset{\displaystyle NH_2}{|}}{P}} - N \underset{\diagdown CH_2CH_2 - X}{\overset{\diagup CH_2CH_2 - X}{}} \quad ,$$

$$\xi - Z - CF_2 - CH_2 - \overset{HF}{\underset{}{C}} - CH_2 - \overset{\overset{\displaystyle O}{\|}}{C} - OH \quad ,$$

$$\xi - Z - CH_2 - \overset{\overset{\displaystyle NH}{|}}{\underset{}{CH}} - \overset{\overset{\displaystyle OH}{|}}{\underset{}{CH}} - CH = \overset{\overset{\displaystyle H}{|}}{C} - (CH_2)_{12}CH_3 \quad ,$$

with the substituent above NH:

$$\overset{CH_3}{\underset{\|}{\underset{C}{\overset{|}{}}}} = O$$

$$\xi - Z - CF_2 - \overset{\overset{\displaystyle CH_3}{|}}{\underset{}{C}} - \overset{\overset{\displaystyle O}{\|}}{C} - OH \quad ,$$

$$\xi - O - \overset{\overset{\displaystyle H}{|}}{N} - \overset{\overset{\displaystyle O}{\|}}{C} - NH_2$$

and

$$\xi\!\!-\!\!Z\!-\!CF_2\!-\!\overset{H_2}{C}\!-\!\overset{\overset{\displaystyle O}{\|}}{C}\!-\!OH \qquad ,$$
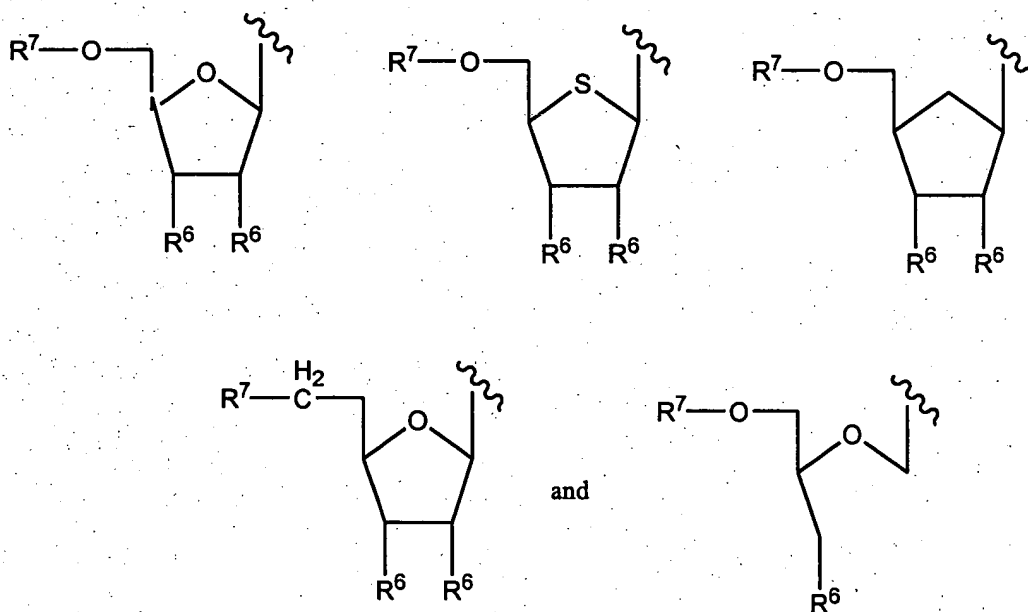
wherein X is -Cl, -Br, -I, or other potent leaving group, with the proviso that when R^7 is -H, and M is zero, then R^4 is not a halogen or when m is zero and n is zero, then R^4 is not a halogen;

wherein Y is independently -H or -F;

wherein Z is independently -O- or -S-;
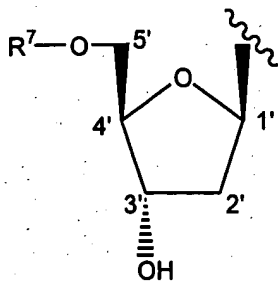
wherein Q is selected from the group consisting of:

and

wherein R^6 is independently -H, -OH, -OC(=O)CH$_3$, or -O-Rg wherein Rg is a hydroxyl protecting group other than acetyl; and,
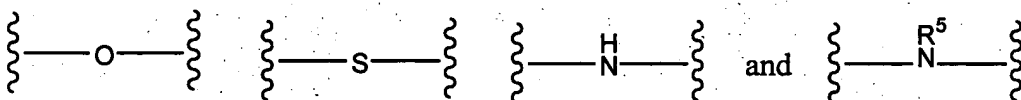
wherein R^7 is selected from the group consisting of hydrogen, a masked phosphoryl moiety and a phosphoramidatyl moiety;

and wherein said compound may be in any enantiomeric, diasteriomeric, or stereoisomeric form, consisting of a D-form, L-form, α-anomeric form, and β-anomeric form.
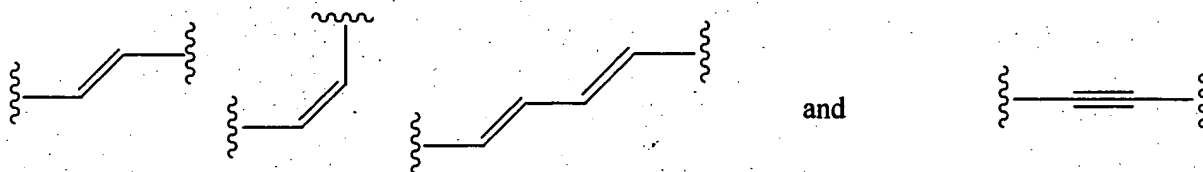
9

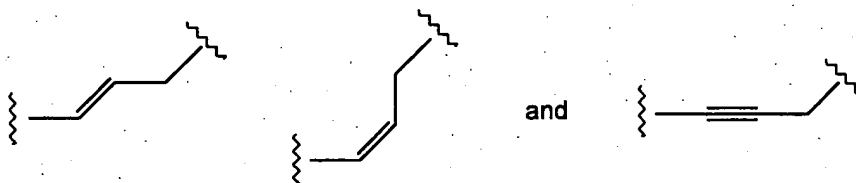63.   (Original) A compound according to claim 62, wherein Q is:

64.   (Previously Amended) A compound of claim 62, wherein R^3 is selected from the group consisting of:
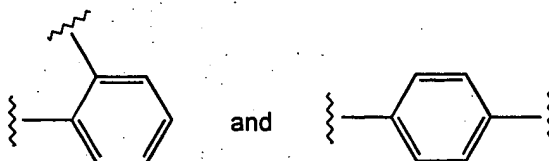

65.   (Previously Amended) A compound of claim 62, wherein R^2 is selected from the group consisting of:

66.   (Original)   A compound of claim 62, wherein R^2 and R^3, taken together form a structure selected from the group consisting of:

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67.   (Previously Amended) A compound of claim 62, wherein R^2 is selected from the group consisting of:

and

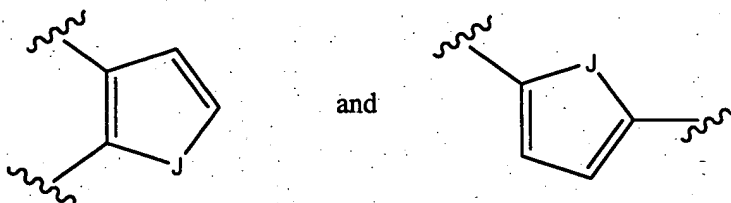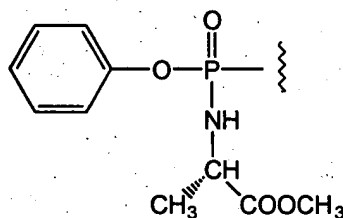68.   (Previously Amended) A compound of claim 62, wherein R^2 is selected from the group consisting of:
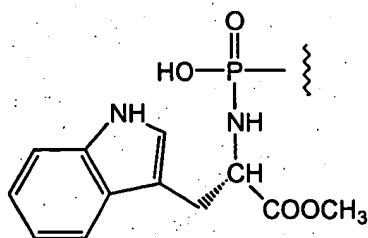

and

wherein J is -O-, -S-, -Se-, -NH-, or -NR^{ALK}-, wherein R^{ALK} is a linear or branched alkyl having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms.

69.   (Previously Amended) A compound of claim 62, wherein R^7 is:

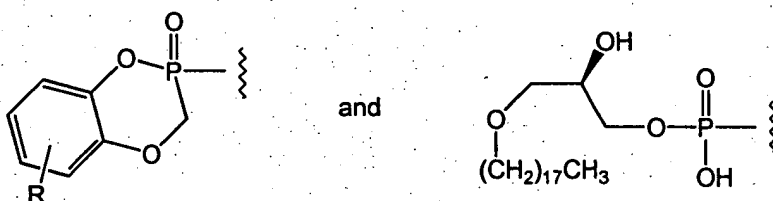70.   (Previously Amended) A compound of claim 62, wherein R^7 is:

71.   (Original) A compound of claim 62, wherein R^7 is selected from the group consisting of:

and
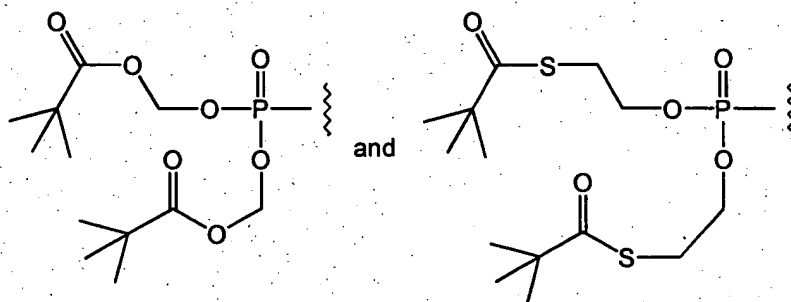
72.   (Original) A compound of claim 62, wherein R^7 is selected from the group consisting of:
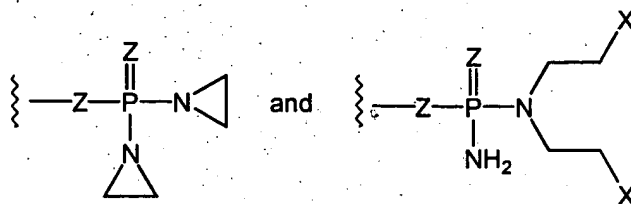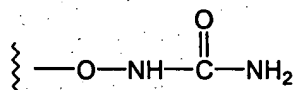

and

73.   (Original) A compound of claim 62, wherein R^4 is selected from the group consisting of:

and

74.   (Original) A compound of claim 62, wherein R^4 is selected from the group consisting of:

$$\{-O-\underset{\underset{N}{|}}{\overset{\overset{O}{\|}}{P}}-N\triangleleft \quad \text{and} \quad \{-O-\underset{\underset{N}{|}}{\overset{\overset{S}{\|}}{P}}-N\triangleleft$$

75.   (Original) A compound of claim 62, wherein R^4 is:

$$\{-O-NH-\overset{\overset{O}{\|}}{C}-NH_2$$

76.   (Currently Amended) A compound of claim 62, wherein R^4 is:

$$\{-Z-CH_2-\underset{\underset{NH}{|}}{CH}-\underset{\underset{OH}{|}}{CH}-CH=CH-(CH_2)_{12}CH_3$$

where the chain bears $\overset{\overset{CH_3}{|}}{\underset{\|}{C}}=O$ above the NH (with "CH₃" amended from "CH₂").

77.   (Original) A compound of claim 62, wherein R^4 is:

$$\{-Z-CF_2-CH_2-CHF-\overset{\overset{O}{\|}}{C}-OH$$

$$\{-Z-CF_2-CHF-CH_2-\overset{\overset{O}{\|}}{C}-OH$$

$$\{-Z-CF_2-CH_2-\overset{\overset{O}{\|}}{C}-OH \quad \text{or}$$

$$\{-Z-CF_2-\underset{\underset{CH_3}{|}}{CH}-\overset{\overset{O}{\|}}{C}-OH$$

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78.   (Original) A compound of claim 62, wherein R^4 is:

$$\xi-Z-CF_2-\underset{\underset{Y}{|}}{\overset{\overset{Y}{|}}{C}}-Y$$
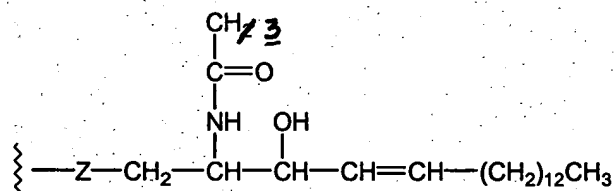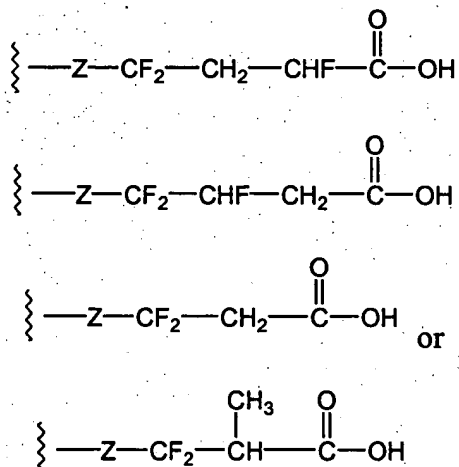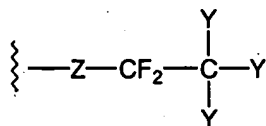
79.   (Original) A compound of claim 62, wherein R^4 is:

$$\xi-Z-CF_2-CH_2-CH_2-NO_2$$
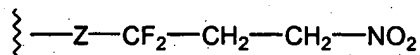
80.   (Currently Canceled).

81.   (Currently Amended) A method for inhibiting the proliferation of a hyperproliferative <u>neoplastic</u> cell, comprising contacting the cell with an effective amount of a compound of claim 62.

82.   (Original) The method of claim 81, wherein the hyperproliferative cell is characterized by the endogenous overexpression of an intracellular enzyme.

83.   (Original) The method of claim 82, wherein the enzyme is thymidylate synthase.

84.   (Currently Amended) A method for treating a pathology characterized by hyperproliferative <u>neoplastic</u> cells in a subject comprising administering to the subject a compound of claim 62.

85.   (Currently Canceled).

86.   (Currently Amended) A method of inhibiting the proliferation of a pathological <u>neoplastic</u> cell that overexpresses an intracellular target enzyme, comprising:

(a) contacting the cell with a compound of claim 62; and

(b) allowing the cell to take-up and selectively convert the compound from an inactive

state to an active toxic by-product by means of the intracellular target enzyme.

87.   (Previously Amended) A method of inhibiting the proliferation of a hyperproliferative cell that overexpresses intracellular enzymes and which contribute to drug resistance, comprising:

(a) contacting the cell with the compound of claim 62; and

(b) allowing the cell to take-up and selectively convert the compound from an inactive state to an active toxic byproduct by means of the enzyme.

88.   (Previously Amended) The method of claims 86 or 87, wherein the hyperproliferative cell is a cancer cell.

89.   (Original)   The method of claim 88, wherein the cancer cell is selected from the group consisting of a colorectal cell, a head and neck cancer cell, a breast cancer cell, a liver cancer cell and a gastric cancer cell.